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Predicting prolonged duration of fever in children:

a cohort study in primary care

Abstract

Background
Fever in children in primary care is commonly caused by benign infections, but often worries parents. Information about the duration of fever and its predictors may help in reassuring parents, leading to diminished consultation of health care.

Aim
To determine which signs and symptoms predict a prolonged duration of fever in febrile children in primary care and evaluate whether C-reactive protein (CRP) measurement has an additive predictive value for these symptoms.

Design and setting
A prospective cohort study at a GPs' cooperative (GPC) out-of-hours service.

Method
Children (aged 3 months to 6 years) presenting with fever as stated by the parents were included. Exclusion criteria were no communication in Dutch possible, previous enrolment in the study within 2 weeks, referral to the hospital directly after visiting the GPC, or no informed consent. The main outcome measure was prolonged duration of fever (>3 days) after initial contact.

Results
Four-hundred and eighty children were analysed, and the overall risk of prolonged duration was 13% (63/480). Multivariate analysis combined model of patient history and physical examination showed that 'sore throat' (OR 2.8; 95% CI = 1.30 to 6.01) and 'lymph nodes palpable' (OR 1.87; 95% CI = 1.01 to 3.49) are predictive for prolonged duration of fever. The discriminative value of the model was low (AUC 0.64). CRP had no additive value in the prediction of prolonged duration of fever (OR 1.00; 95% CI = 0.99 to 1.01).

Conclusion
The derived prediction model indicates that only a few signs and symptoms are related to prolonged duration of fever. CRP has no additional value in this model. Overall, because the discriminative value of the model was low, the duration of fever cannot be accurately predicted.

Keywords
child; child, preschool; family practice; fever; infant; primary care; signs and symptoms.

INTRODUCTION

Fever in children is a common reason for parents to contact a GP.[1] It is a common symptom in children, often caused by benign infections with no need for medical intervention. Little is known about the natural course of fever in children,[2,3] and (prolonged) duration of fever before presentation to health care has no well-established predictive value for the presence of a serious bacterial infection.[4,5] However, health-related quality-of-life is reported to be significantly lower in febrile children who remained febrile after ≥7 days.[6] Therefore, prolonged duration of fever seems to play an important role in perceived health. A longer duration of fever in children is related to return visits to the emergency department (ED) and concerns about fever may contribute to a significant number of return visits to the ED.[7] Parents may have significant concerns about the potential adverse effects of fever; a phenomenon also known as 'fever phobia'.[8,9] Knowledge of the expected duration and the signs and symptoms that are related to prolonged duration of fever may be helpful in informing and instructing patients or parents, resulting in more efficient healthcare use. Educating parents about the expected duration of fever may lead to a reduced rate of returning to medical care, without increased health risk.

In addition to this, the value of measuring C-reactive protein (CRP) in febrile children is not clearly established in primary care.[10] In adult patients with acute cough, however, it is shown that CRP can help in reassuring both patient and GP that antibiotics are not indicated.[11–13] CRP may help identify febrile children that remain febrile over a longer period. This may help in informing the parents and prevent unnecessary reconsultations.

In this context, the predictive value of signs and symptoms for prolonged duration of fever in febrile children presenting at a GP cooperative (GPC) out-of-hours service were assessed, and the additive value of CRP to these signs and symptoms was determined when predicting prolonged duration of fever.

METHOD

This cohort study was performed at a GPC out-of-hours service in Rotterdam, a large multiethnic city in the Netherlands. This GPC covers an area encompassing approximately 300 000 inhabitants.

Study procedures

Between December 2004 and January 2006 during Monday through Thursday, in the evenings and night, consecutive children

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How this fits in

Although a longer duration of fever has no clear established predictive value for serious infections, it may lead to parental concern and, subsequently, increased medical care consumption. To inform and instruct parents, more knowledge of the expected duration and the signs and symptoms that are related to prolonged duration of fever may be helpful. This study found several signs and symptoms to be related to a prolonged duration of fever. The overall predictive value was low, however, so the duration of fever cannot be predicted for an individual patient.

were included if they were aged between 3 months and 6 years, and presented with fever as stated by the parents. Fever had to be reported during the first contact, regardless of the presence or absence of accompanying signs and symptoms. Children were excluded if communication in Dutch was impossible, if the child had already been enrolled in this study in the previous 2 weeks, if the child was referred to the hospital directly after visiting the GPC, or if the parents declined to give informed consent.

When parents contacted the GPC by telephone concerning their febrile child, the receptionists performed the standard triage based on the triage guideline of the Dutch College of General Practitioners (NHG).[14] Based on this triage, parents received either telephone advice, or the advice to attend the GPC out-of-hours service (physical consultation), or a home visit by a GP was arranged. The GPs were free to prescribe treatments of their own choice, or to refer the child.

Measurements

For the purpose of this study, for all children, an additional home visit by a trained research nurse was arranged within 24 hours of inclusion. Using a structured questionnaire, the research nurse recorded demographic data, signs and symptoms, physician contacts, and prescribed medication, as reported by the parents. In addition, a standardised physical examination (including rectal temperature) was performed.

Dyspnoea was defined as an elevated respiratory rate, taking age into account,[15] and nasal flaring, or chest wall retractions. The score on the Yale Observation Scale (YOS) was part of the structured physical examination; this has a 6-item score used to predict the severity of illness in febrile children.[16] Duration of fever previous to the consultation with the GPC was determined in days and calculated using the date of contact, and the date of the first recognised fever. During the home visit, capillary blood was obtained to measure CRP values (NycoCard™ CRP test, Clindia Diagnostics, Leusden, the Netherlands).[17] Values of CRP measurements ranged from 8 to 250; for the purposes of analysis, values <8 and >250 were considered to be 7 and 251, respectively.

Follow-up

Parents received a thermometer and a demonstration of how to use it. Using a structured diary during 1 week, parents reported rectal temperature twice a day and, once a day, details of symptoms, medical care contacts, and use of antibiotics. Diaries were returned to the researchers by post. Fever was defined as a rectal temperature of ≥38.0°C.

Outcome measurement

The main outcome measure was prolonged duration of fever (>3 days), measured by a rectal thermometer and consequently reported by the parents in the diaries, starting on the day of the home visit. A duration of >3 days was chosen as a definition for prolonged duration of fever, as the Dutch guideline for feverish children states that children with this duration need physical assessment by a physician.[18] Duration of fever was calculated per day. Temperature was measured twice a day, if one of those measurements was ≥38.0°C, the child was considered to have fever during that day. When a diary was not completed, but the child was not febrile on the last-notated day, it was assumed that the child had recovered from the fever. When data were insufficient to calculate duration of fever, multiple imputation was performed using the data available from the diaries, and from the patient history and physical examination. Within this period, febrile episodes with one 'fever-free' day were considered to be one episode. When there were two fever-free days, the next day with fever was considered to be a new episode; this new episode was not incorporated in the analyses (n = 27).

Statistical analysis

Patient characteristics and frequency of prolonged duration of fever were analysed using descriptive statistics. Variables possibly related to prolonged duration of fever were analysed with bivariate and

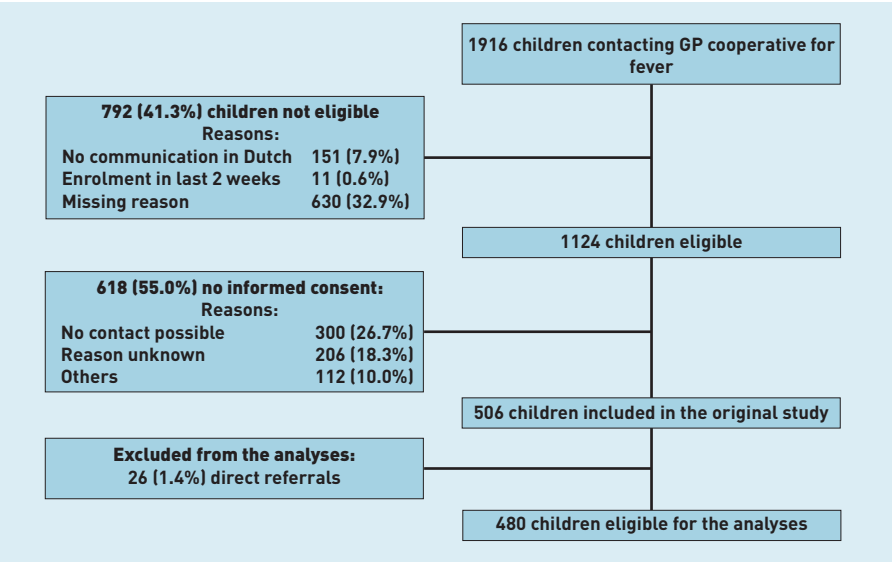

Figure 1. Flowchart of the eligible children.

multivariate logistic regression. First, variables showing a bivariate statistical association of $P<0.157$ (Appendix 1)[19] were entered into multivariate models concerning separate patient history, and physical examination. Second, variables with a multivariate statistical association of $P<0.157$ with prolonged fever were combined in one model. Manual backward logistic regression was performed on this model using a cut-off of $P<0.157$, adjusting for duration of fever before consultation. If multicollinearity was present between similar variables in patient history and physical examination (suspected when large changes occurred in the estimated regression coefficients when a variable was entered or deleted from the model), the variable concerning physical examination was dropped. Duration of fever before contact with the GPC was added to the multivariate model to adjust for confounding; additionally, antibiotic prescription at the GPC was tested for possible confounding by adding this to the final model and to search for significant changes in the ORs. Finally, CRP was added to this model to determine the additive value. The discriminative ability of both models was assessed using the area under the receiver operating characteristic curve (AUC). Missing data were imputed using multiple imputation.[20] Multiple imputation was performed using MICE in R-2.11.1 for Windows. Data were analysed using SPSS (version 17.0.2).

Table 1. Characteristics of the study population (*n* = 480)

Characteristics	*n/N*	%
Age, months		
3–<6	35/480	7.3
6–<12	95/480	19.8
≥12	350/480	72.9
Rectal temperature ≥38.0°C	154/480	32.1
Ill appearance	43/480	9.0
Duration of fever, days	**Median**	**IQR**
Before consultation	2	1–3
After consultation	1	0–2

IQR = interquartile range. The physical examination forms included categorical variables with possible answers: 'no, little, very, very much'. These variables were dichotomised using a cut-off point between 'little' and 'very'.

Sample size calculation

An $\alpha<0.157$ was chosen to include variables in the model. With a 5:1 ratio of absence to presence of the sign and symptom under investigation with prolonged duration, and an average of 13% prolonged duration in the group without the variable under investigation, a power of 0.80 to find an OR of 2.00, 459 children were needed in the analysis.

RESULTS

Description of the population

A total of 506 children were included in the original cohort. Of these, 134 received telephone advice 26.5%), 26 were directly referred to the hospital and excluded from this analysis, leaving 480 eligible children (Figure 1). For 162 children the duration of fever after consultation could not be directly calculated (because of incomplete diaries) but was estimated using multiple imputation. Median age of the included children was 21 months (IQR 10–38 months). Median rectal temperature at the time of assessment was 37.6°C (IQR 37.0–38.1°C). In total, 63 children had fever lasting >3 days. Median duration of fever after initial contact with the GP was 1 day (IQR 0–2, follow-up was limited to 7 days). Median duration of fever before consultation was 2 (IQR 1–3) days. Additional patient characteristics are presented in Table 1.

Bivariate logistic regression

Bivariate logistic regression showed that most of the signs and symptoms were not related to prolonged duration of fever (Appendix 1). CRP showed a bivariate OR of 1.00 (95% CI = 0.99 to 1.01).

Multivariate logistic regression

Multivariate logistic regression for patient history showed that 'sore throat' (OR 2.26, 95% CI = 1.17 to 5.37) was significantly ($P<0.157$) associated with prolonged duration of fever (Table 2). The multivariate logistics regression for physical examination

indicated that 'signs of throat infection' (OR 2.21, 95% CI = 1.10 to 4.41) and 'lymph nodes palpable' (OR 1.74, 95% CI = 0.92 to 3.27) were related to prolonged duration of fever (Table 3).

The combined model of both patient history and physical examination showed that 'sore throat' (OR 2.80, 95% CI = 1.30 to 6.01) and 'lymph nodes palpable' (OR 1.87, 95% CI = 1.01 to 3.49) were predictive for prolonged duration of fever (Table 4). Of all the children, 34% with sore throat and palpable lymph nodes had a prolonged duration of fever compared with 11% of the children with none of these signs. The mean AUC was 0.64 (SD 0.02). CRP showed no additive value to this model for predicting prolonged duration of fever (OR 1.00, 95% CI = 0.99 to 1.01), with the mean AUC remaining at 0.64 (SD 0.03). Table 5 shows the individual relation of the signs and symptoms of the final model with prolonged duration of fever.

Table 2. Multivariate analysis of variables concerning patient history

Variables	OR	95% CI	*P*-value
Diarrhoea	1.60	0.82 to 3.09	0.17
Moaning	1.50	0.80 to 2.81	0.21
Earache	1.49	0.73 to 3.06	0.28
Sore throat	**2.51**	**1.17 to 5.37**	**0.02**

OR = odds ratio. Bold = P<0.157. The patient history forms included categorical variables with possible answers: 'no, little, very, very much, and do not know'. These variables were dichotomised using a cut-off point between 'little' (including 'do not know') and 'very'.

Table 3. Multivariate analysis of variables concerning physical examination

Variables	OR	95% CI	*P*-value
Palpable lymph nodes	**1.74**	**0.92 to 3.27**	**0.09**
Sign of throat infection	**2.21**	**1.10 to 4.41**	**0.03**
Rectal temperature >38.0°C	1.76	0.79 to 3.95	0.18

OR = odds ratio. Bold = P<0.157. The physical examination forms included categorical variables with possible answers: 'no, little, very, very much'. These variables were dichotomised using a cut-off point between 'little' and 'very'.

Table 4. Prediction model for prolonged duration of fever, with and without CRP

Variables	OR	95% CI	P-value	OR	95% CI	*P*-value
Sore throat (PH)	2.80	1.30 to 6.01	0.01	2.81	1.30 to 6.04	0.01
Palpable lymph nodes (PE)	1.87	1.01 to 3.49	0.05	1.87	1.00 to 3.49	0.05
Duration of fever before consultation (PH)	0.93	0.79 to 1.10	0.39	0.93	0.79 to 1.10	0.40
CRP				1.00	0.99 to 1.01	0.89
Area under the curve (mean, SD)	0.64 (0.02)			0.64 (0.03)		

CRP = C-reactive protein. OR = odds ratio. PE = physical examination. PH = patient history. Multicollinearity: there was multicollinearity between 'sore throat' and 'signs of throat infection'. Therefore, the variable concerning physical examination ['signs of throat infection'] was dropped. The patient history forms included categorical variables with possible answers: 'no, little, very, very much, and do not know'. These variables were dichotomised using a cut-off point between 'little' (including 'do not know') and 'very'. The physical examination forms included categorical variables with possible answers: 'no, little, very, very much'. These variables were dichotomised using a cut-off point between 'little' and 'very'.

Table 5. Signs and symptoms of the final multivariate model and their relation with prolonged duration

	Prolonged duration of fever	
Signs and symptoms included in analysis	**Sign present, %**	**Sign absent, %**
Sore throat	25 (18/72)	11 (45/408)
Palpable lymph nodes	17 (36/208)	10 (27/272)
Duration of fever before consultation	N/A	N/A
CRP	N/A	N/A

CRP = C-reactive protein. N/A = not applicable.

DISCUSSION

Summary

The present study shows that, for children not directly referred to secondary care, the median duration of fever after consultation with the GPC is 1 day. The multivariate analysis showed that sore throat and palpable lymph nodes were predictive for a duration of fever >3 days. The predictive value of the model was considered low (AUC 0.64). CRP had no additive predictive value for prolonged duration of fever.

Besides duration of fever before contact with the GPC, antibiotic prescription at the GPC was added to the model to control for potential confounding (data not shown). However, for reasons of clarity this was removed from the model, as it had no influence. Duration of fever before consultation with the GPC was not significantly related to prolonged duration of fever. It was expected that a relation would be found between the duration of fever as reported on consultation and the duration of fever in the follow-up. However, a straightforward relation may not be applicable in this setting because of the broad variation in duration of fever in children in primary care.[2]

Strengths and limitations

This large cohort study provides data on duration of fever in children in primary care. Its structured patient history, physical examination, and prospective data collection on the duration of fever, provide valuable and detailed data on the course of fever in children in primary care. To the authors' knowledge, this is the only prospective cohort of febrile children in primary care with a follow-up of 7 days.

A limitation of the present study is that the research nurse noted the patient's history and made the physical examination the day after the patient had made contact with the out-of-hours service. This study design

was chosen so as not to interfere with the regular care of the out-of-hours service (especially in the case of telephone advice without face-to-face contact).[2,21] Some signs may have altered over the short period between initial consultation and the home visit by the research nurse (such as, YOS, ill appearance, dyspnoea, capillary refill, chin on chest, and rectal temperature ≥38.0°C). However, the research nurse specifically asked for the symptoms that were present at the time of consultation with the out-of-hours service. In addition, the median time that elapsed between time of consultation with the out-of-hours service and the home visit was only 14.5 hours. It is believed that the median duration of 14.5 hours between initial contact and the home visit did not alter significantly the presence or absence of the remaining signs (such as, coughing, rhinorrhoea, palpable lymph nodes, signs of throat infection, or earache resulting in altered reaction or sleeping pattern).[22]

A further limitation is the substantial loss to follow-up; that is, insufficient data to calculate duration of fever. A complete-case analysis was performed with the final model, showing a stronger relation of the included variables to prolonged duration of fever (data not shown). This problem was solved using multiple imputation; moreover, as multiple imputation is considered the most appropriate way of dealing with missing data,[23] only the imputed results are presented here.

An α<0.157 was chosen to include variables in the model. For sufficient power, 459 children were needed in the analysis. However, for variables with a ratio of absence:presence of the signs and symptoms under investigation higher than 5:1 the study may have been underpowered when the OR was <2.00 (that is, signs and symptoms present <80 times). However, when a symptom is very uncommon, it cannot be a good predictor for the more common prolonged duration of fever. Therefore, it is believed no important predictors of prolonged duration were 'missed'.

The present study did not look for any relation between (working) diagnosis and prolonged duration of fever. This is because GPs make diagnostic transfers to diagnoses that justify their policy,[24] therefore these diagnoses are ultimately related to the signs and symptoms of the presenting febrile child. Investigating the relation between signs and symptoms and prolonged duration of fever seems more appropriate.

Comparison with the existing literature

In this study, sore throat had a predictive value for prolonged duration of fever. Other studies also have reported that 60% of patients with a sore throat still have complaints after 3 days,[25] and the duration of acute tonsillitis is approximately 5 days.[26] This is in line with the present findings. An acute infection (for example, otitis media) has a relatively short symptomatic period with a median duration of fever (as well as earache) of around 3 days. This is closer to the present cut-off for prolonged duration and, therefore, had no predictive value in the present model. A review of the duration of symptoms of respiratory tract infections reported similar trends; 28% of the children with sore throats had fever for ≥3 days.[22]

Implications for research

The derived model had a low predictive value for prolonged duration of fever. The median AUC was only 0.64 (SD 0.02), indicating that the performance of the model is suboptimal. Therefore, with this model it is not possible to make a valid prediction as to whether children will or will not have prolonged duration of fever.

As prolonged duration of fever cannot be predicted, other methods to reassure both parents and GPs should be further investigated. Safety netting is not well defined in primary care, and research on the methods and efficacy is needed, but should include information about the uncertainty of the diagnosis, when and how to seek reconsultation, and what the expected course of the illness will be.[27–30] This safety netting may help to reduce the number of unnecessary reconsultations.

In this primary care cohort, CRP had no additional value for predicting prolonged duration of fever. Further research is needed to determine the additive role of CRP in managing febrile children in primary care, for example the predictive value for serious infections, support regarding whether or not to prescribe antibiotics, and/or the planning of scheduled revisits.

In conclusion, although a few signs and symptoms are predictive for a prolonged duration of fever, the discriminative value of the model is low. It is of interest to know that fever in children has a median duration of 4 days,[2] but, at present, prolonged duration of fever in any individual patient cannot be predicted.

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Ethical approval

The study was approved by the Dutch Central Committee on Research Involving Human Subjects.

Provenance

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Competing interests

The authors have declared no competing interests.

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Appendix 1. Bivariate analyses of signs and symptoms and prolonged duration of fever

Patient history (Signs present at moment of contacting OOH service)	Sign present, %	Sign absent, %
Duration of fever prior to contact	NA	NA
Different illness than usual	15 (39/261)	11 (24/219)
Inconsolable crying	13 (29/222)	13 (34/258)
Crying during diaper change	13 (18/143)	13 (45/337)
Crying when picked up	12 (16/139)	14 (47/341)
Diarrhoea	**18 (21/117)**	**12 (42/364)**
Vomiting	16 (26/160)	11 (36/321)
Drowsy/difficult to wake	11 (27/237)	15 (36/243)
Pale/grey/spotted skin	12 (29/239)	14 (34/241)
Skin rash	12 (12/98)	13 (51/382)
Moaning	**16 (37/230)**	**10 (26/250)**
Febrile seizure	26 (7/27)	12 (55/453)
Comorbidity	11 (11/96)	14 (52/384)
Age, months	NA	NA
Played as usual	14 (40/283)	12 (23/197)
Normal reaction to parents	10 (4/42)	13 (59/438)
Restless/confused	14 (20/141)	13 (43/339)
Irritable/irritated	16 (28/172)	11 (34/308)
Drinking less than half than usual	14 (24/172)	13 (39/308)
Ear ache	**18 (15/82)**	**12 (47/398)**
Runny nose	15 (24/158)	12 (39/322)
Coughing	15 (25/163)	12 (38/317)
Sore throat	25 (18/72)	11 (45/408)
Abdominal pain	18 (14/78)	12 (49/402)
Concerned parents during home visit	18 (15/82)	12 (47/398)
Physical examination		
Yale Observation Scale	NA	NA
Ill appearance	17 (7/42)	13 (56/438)
Coughing	16 (29/179)	11 (34/301)
Rhinorrhoea	12 (31/257)	14 (32/223)
Dyspnoea	14 (19/140)	13 (43/340)
Capillary refill (>2 seconds)	13 (4/31)	13 (59/449)
Palpable lymph nodes	**17 (36/208)**	**10 (27/272)**
Chin on chest	5 (1/21)	13 (61/459)
Rectal temperature ≥38.0°C	**18 (28/154)**	**11 (35/326)**
Signs of throat infection	**20 (33/166)**	**10 (30/314)**
Earache resulting in altered reaction or sleeping pattern	21 (8/38)	12 (55/443)
C-reactive protein	NA	NA

Bold = P<0.157. NA = not applicable because of continuous variable. OOH = out of hours. The history and physical examination forms included categorical variables with possible answers: 'no, little, very, very much'. These variables were dichotomised using a cut-off point between 'little' and 'very'. Categorical variables with possible answers: 'no, little, almost normal, normal' were dichotomised using a cut-off point between 'no' and 'little'. Diarrhoea was characterised as reported diarrhoea more than twice a day. Comorbidity was considered positive when the child was under treatment of a paediatrician or ENT-physician.